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Exposure and susceptibility: Schizophrenia in a young man following prolonged high exposures to organic solvents

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ABSTRACT

There is an abundant literature on the adverse effects of solvents on the neurobehavioral performance, higher brain functions, and chronic solvent-induced encephalopathy. However, the occurrence of solvent-related schizophrenia is rare, with few reports on the link between solvent exposure and schizophrenia. Here, we report on a patient with schizophrenia, presenting after a sustained period of 6 months of everyday exposure to neurotoxic solvents in an unprotected occupational setting in Haifa, Israel. In light of the similarity of symptoms of schizophrenia and chronic solvent encephalopathy, we call for further epidemiologic studies to examine the potential contribution of solvent exposure to the etiology and evolution of schizophrenia in selected cases. This case study and review of relevant literature underscores the importance of obtaining detailed histories on occupational exposures to search for agents which can trigger psychotic episodes. In the meantime, policies to prevent such exposures at the source can be expected to contribute to the prevention of a non-trivial proportion of neurotoxic diseases, including, possibly, schizophrenia in worker populations.

1. Introduction

There is an abundant literature on the deleterious effects of solvents on the neurobehavioral performance, higher brain functions and chronic solvent-induced encephalopathy. But literature establishing a cause–effect relationship between solvent exposure and schizophrenia is sparse, consisting mostly of case reports, case series reports, and cross sectional comparisons (see literature review and Tables 1 and 2).

Schizophrenia is defined as any of several psychotic disorders characterized by distortions of reality, impairments of thought and language and withdrawal from social contact (Mueser and McGurk, 2004). The disease is traditionally considered to be triggered by unknown factors intrinsic to the patient. Few studies have focused on occupational exposures as possible causes of schizophrenia. As with other diseases, the pathogenesis and clinical expression of schizophrenia may involve gene–environment interactions and genetic susceptibility (Tsuang et al., 2004; Caspi and Moffitt, 2006). Here, we report on a patient with schizophrenia, first diagnosed with acute psychosis which was precipitated by a sustained period of exposures to neurotoxic solvents in an occupational setting.

2. Case report

The patient was a 30-year-old man, the 9th of 10 siblings, son of a 43-year-old father and 35-year-old mother at the time of his birth. His family immigrated to Israel from Tajikistan. The patient was hospitalized in November 1997 at the age of 24 for an acute attack of what was diagnosed as severe psychosis, subsequently requiring several months of hospitalization. He presented in the Emergency Room with acute delirium, disorganized and violent behavior, and was agitated, restless, and unable to restrain himself, with fits of shouting and crying, suicidal thoughts, unsteady gait, muscle pain and insomnia. On neurological examination, he was found to have horizontal nystagmus, which later disappeared. During this period before hospitalization, his family, including his mother, noted that he behaved as though he were drunk, even though he was a teetotaler. His family denied abuse of hashish or alcohol, including vodka, to which he said he was allergic. His family, at that time, was unaware of occupational exposures to potentially toxic compounds.

The behavioral change was gradual. In the weeks and months prior to hospitalization, he experienced irritation of skin and airways.

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The conjunctivae in his eyes were noted to be red; his skin color was described as yellow. He suffered from headaches, dizziness, nausea, fatigue, irritability, forgetfulness, and loss of appetite. He felt depressed and agitated. His speech was slurred and its content was incoherent, as though drunk. His urine was dark in color.

Serum transaminase levels were elevated and mild thrombocytopenia was detected on his first hospitalizations.

3. Occupational history

The patient's psychotic attack occurred following 6 months of work in a paint factory, beginning in May 1997, where he was exposed for up to 17 h a day to paints and many organic solvents, in a closed small caravan 12 m^3 in volume. He worked as a painter of computer metal components, in a small room containing a stove, a waterfall device for absorbing droplets of paint, and two chimneys. Among the agents were toluene, xylene, n-butyl acetate, ethylene glycol, monomethyl ether acetate, methoxy propranole, trimethylbenzene, iso-butanol, as well as organic and inorganic pigments, strontium chromate, lead and acetone. There were severe dermal and respiratory exposures at extremely high levels, under extremely poor working conditions. There were neither windows nor ventilation systems in his working environment. His work consisted of spraying the paints on to the electronic components and cleaning the equipment by immersing it in acetone by his bare hands. He had no gloves to use. He used a non-protective cotton face mask which he received from his employer. He ate alone in the caravan and had not been informed on the exposures and possible health risks. No surveys or environmental measurements had been performed at the workplace.

Prior to employment, he had been healthy, strong and alert. He completed high school, where he was popular and excelled in sports. Given his high military medical profile, he served full compulsory service in the Israeli Defense Forces (IDF) as a combat solider in an infantry unit from which he was honourably discharged.

4. Family history

A twin sister had died soon after birth, in Tajikistan. A 20-year-old brother was found dead after disappearing, 1 year after immigrating to Israel, without a known prior psychiatric history. A mental health diagnosis of the patient's brother had not been performed.

It was a tightly knit family. His sister, especially, was extremely supportive. We had no information on any problems with crime, drugs or violence in the family.

5. Diagnosis and course

The patient's first discharge diagnosis was acute psychotic state, either from toxic (organic) or functional (non-organic) cause. In the following years, although he was no longer exposed to solvents or other toxic substances, the patient was repeatedly hospitalized due to severe psychotic attacks, in which he became violent and required restraint. Between psychotic episodes he did not resume his former high level of function but was mostly idle, secluded and withdrawn. At some point there was also a failed marriage. In February 2000 he was hospitalized again and the diagnosis of schizophrenia was first established.

When examined by us in 2003, at the age of 30, the patient was spending much of his time in bed. He was found to suffer from concentration difficulties, especially when reading, and was described by his psychiatrists as lacking motivation (abulia), suffering from chronic fatigue and depressed. On physical examination, he appeared apathetic, there were no disturbances in organization of thoughts, concepts, judgment and perception, and there was no disorientation in relation to time, place or self. He required sedatives, antidepressants and tranquilizers.

The patient underwent a comprehensive neurocognitive assessment in 2003. Memory was evaluated using the Wechsler Memory Scale (Wechsler, 1945; Cohen, 1950). His learning capacity skills were tested using the Rey Auditory Verbal Learning test. Our patient showed impairment, particularly in immediate working memory. His scores were two standard deviations below the norm and his learning curve I–V was very flat: trial I = 3, II = 5, III = 8, IV = 8, and V = 8. Such low scores probably reflect, at least partly, the effort invested in performing the tests rather than true cognitive abilities. Lack of volition is regarded as a "negative sign" of schizophrenia and frontal subdominant organic brain damage, as well as a clinical feature of depression. His physicians and close family members have reported a slight improvement in his memory since.

Repeated electroencephalographies (EEGs) and magnetic resonance imaging (MRI) brain scans showed unremarkable findings, but these tests were performed 3 years after his acute exposures, by which time the acute effects on electrophysiological parameters of brain function, would not necessarily have persisted. The absence of findings on imaging is consistent with experience that imaging procedures cannot be relied upon as gold standard tests of brain disease from toxic exposures (Lubman et al., 2002). Furthermore, EEG reflects first and foremost the electrical cortical activity, while functional solvent-induced impairment is mainly in the subcortical long tracts and associative neural pathways.

Fig. 1 presents a timeline tracking course of the patient's illness.

6. Literature review

Table 1 presents case reports and case series studies, relevant to exposure to solvents, which discuss a range of neurological and psychiatric outcomes, including schizophrenia. These are relevant to our case report, because (1) they have richness in individual detail lacking in larger analytic studies, (2) they enable us to relate our findings to those from prior knowledge, and (3) they also generate hypotheses for testing interesting associations, relevant to our hypothesis regarding exposure and susceptibility.

Wada et al. (2005) compared a group of solvent-exposed patients and a group of schizophrenic patients. Overlap in signs and symptoms between patients diagnosed as having solvent-induced psychosis and patients with schizophrenia is described; these include delusion, hallucination, anxiety, emotional instability and loss of motivation. It is interesting to note that the symptom of loss of motivation, characteristic of patients suffering from solvent-induced psychosis is very similar to the negative signs typical to schizophrenia.

Case–case reports are interesting in that they suggest, by analogy, the possibility that exposures that lead to syndromes somewhat similar to schizophrenia, can also lead to schizophrenia.

Case-referent studies face the difficulty of selecting comparisons. Daniels and Latcham (1984) presented 29 male and 5 female schizophrenic patients, from an island in which self-induced exposure to solvents is common (petrol sniffing). Compared to matched referents, the schizophrenic patients had a much higher probability of past exposure to solvents—an association which suggests the possibility of a cause–effect relationship.

Cohort studies: Cohort-type studies are presented in Table 2. Schizophrenia is difficult to capture in prospective cohort studies because of the relatively low prevalence of the condition – 1% (Mueser and McGurk, 2004), yet large population-based cohorts have managed to extract suggestions of increased risks for schizophrenia with prior exposures to solvents and other agents (Opler et al., 2004), twin status (Kleinhaus et al., 2008), and older age of father (Malaspina et al., 2001) – all of which are relevant to this patient. Two large birth cohorts were followed, a registry of 12,094 births between 1959 and 1966 from Oakland, California

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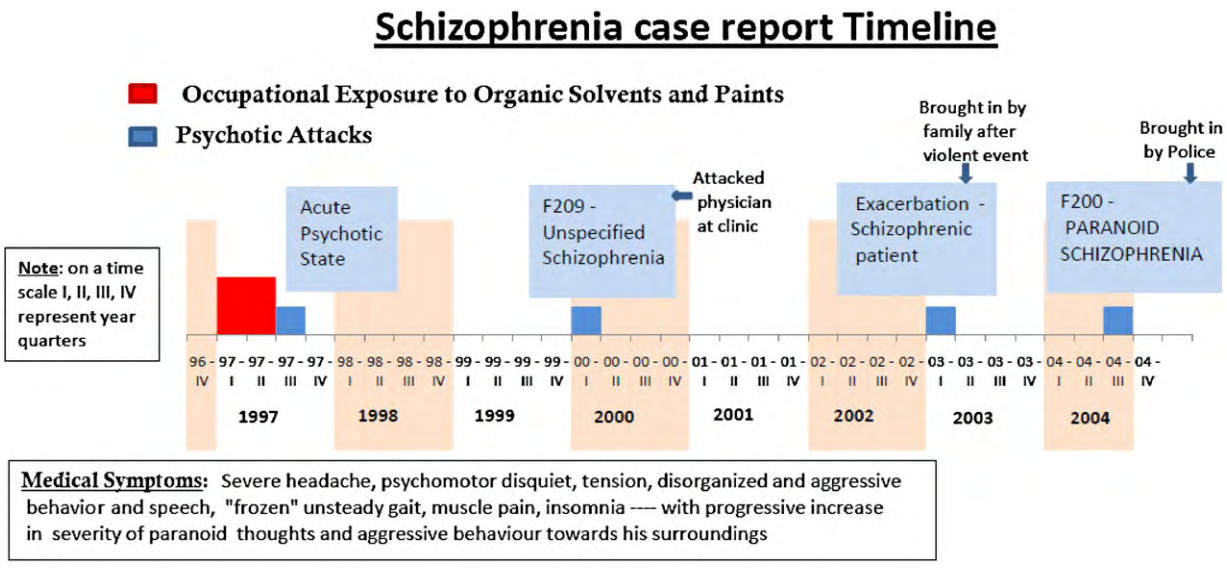

Fig. 1. Timeline of exposures versus medical symptoms.

(Opler et al., 2004), and a registry of 88,829 births between 1964 and 1976 from Jerusalem (Harlap et al., 2007; Perrin et al., 2007).

Mikkelsen (1997) reviewed epidemiologic studies of occupational mixed solvent exposure for evidence of exposure-related neuropsychiatric disorders, mental symptoms, and impaired neurobehavioral performance. Although the reviewed psychiatric morbidity studies did not find a clear relation between occupational solvent exposure and admission to a hospital for psychiatric illness, the author concluded that the cumulative findings strongly suggest that occupational solvent exposure may be the cause of mental and cognitive impairment, which may become chronic and disabling.

Several studies have described patients presenting with signs and symptoms which were also seen in our patient following exposure to solvents, i.e. depressed mood, anxiety, irritability and aggressive behavior. The patients were later diagnosed as chronic solvent encephalopathy (CSE) (Bast-Pettersen, 2009; Juntunen,

Table 1
Case reports and case series studies.

Ref.	Study design and population	Exp.	Outcome	Comment
Rao et al. (2009)	Case report	Chronic abuse of toluene	Psychosis, including delusions of persecution and auditory hallucinations, and irreversible toxic maculopathy	Diagnosis was volatile solvent dependence, solvent-induced, schizophrenia-like psychotic disorder
Saito et al. (1997)	9 patients with solvent psychosis	Solvents	6 patients—Schneiderian first rank symptoms (auditory hallucinations, delusions of control, delusional perception) Of these, 5 patients also had second rank symptoms of hallucinations	Psychosis is a symptom and schizophrenia is a disease. However, most psychotic patients suffer from schizophrenia
Bowler et al. (1992)	Case series 63 former microelectronics workers (56 women, 7 men) Standard version of the Minnesota Multiphasic Personality Inventory (MMPI) to evaluate affective and personality disturbance	Solvents	Mean scale score elevations beyond two standard deviations above the normative sample (T = greater than 70) on the MMPI clinical scales of schizophrenia, hypochondriasis, psychasthenia, depression and hysteria	The authors suggest cause–effect relationship between these women workers' occupational exposures to organic solvents and affective and personality disturbances, consistent with organic solvent toxicity, persistent over a 2-year period
Byrne et al. (1991)	Case series of a group of 22 patients	Chronic histories of solvent abuse, primarily toluene-based solvents	Paranoid psychosis which may persist, high incidence of temporal lobe epilepsy and decrease in IQ	Authors suggest that psychiatric and neurological sequelae of chronic solvent abuse are serious and potentially irreversible
Goldbloom and Chouinard (1985)	Case report	5 years of continuous occupational exposure to toluene	Irreversible schizophreniform psychosis	"Schizophreniform psychosis" is a temporary diagnosis that can be applied for no more than 6 months—after that, particularly if the situation is irreversible, it should be given a definitive diagnosis, either schizophrenia or psychotic disorder due to a General Medical Condition

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Table 2
Cohort-type studies.

Ref.	Study design and population	Exp.	Outcome	Comment
Opler et al. (2004)	Cohort of live births—12,094 babies 44 cases 74 controls	Lead Biomarker—δ-aminolevulinic acid (δ-ALA) Schizophrenia in offspring of parents exposed to lead	Odds ratio (OR) for schizophrenia associated with higher δ-ALA: 2.43 95% CI, 0.99–5.96; $p = 0.051$	Occupational and environmental exposures of parents
Perrin et al. (2007)	The Jerusalem Perinatal Study cohort—88,829 babies 144 offspring of parents in dry-cleaning industry (63 females, 81 males) 4 cases of schizophrenia (2 females, 2 males)	Tetrachloroethylene	Increased incidence of schizophrenia in offspring of male and female parents who were dry cleaners (RR = 3.4, 95% CI, 1.3–9.2, $p = 0.01$)	
Kleinhaus et al. (2008)	The Jerusalem Perinatal Study cohort 2124 twins 87,955 singletons	Assess the role of twin pregnancies as a possible risk factor for schizophrenia	Relative risk for schizophrenia among twins was found to be similar to the general population	
Malaspina et al. (2001)	The Jerusalem Perinatal Study cohort 1337 offspring admitted to psychiatric units before 1998, 658 diagnosed as having schizophrenia and related nonaffective psychoses	Assess the role of paternal and maternal age as a possible risk factor for schizophrenia	Compared with offspring of fathers younger than 25 years, paternal age of 45–49, and of 50 years or more, was a strong and significant predictor of the schizophrenia diagnoses, but not of other psychiatric disorders No effect of maternal age	The relative risk of schizophrenia increased monotonically in each 5-year age group, reaching 2.02 (95% confidence interval, 1.17–3.51) and 2.96 (95% confidence interval, 1.60–5.47) in offspring of men aged 45–49 and 50 years or more, respectively

1993; Keski-Säntti et al., 2009; Saddik et al., 2009). These studies do not present patients with psychotic signs and symptoms, and do not address a possible outcome of schizophrenia.

Bolla et al. (1990) looked at neuropsychiatric symptoms in paint manufacturers. This paper examined all 187 participants with the Present State Exam, a structured psychiatric interview. Exposure data were thorough and complete, and statistical analyses focused on cumulative dose-response relationships. An outcome of depression was found to be significantly related to solvent exposure, and there were other non-trivial associations. The Q16 and exposure data in this paper suggest that even in the highest of four exposure groups, exposures were much lower than those in our patient. These higher exposures in our patient may account for the greater spectrum and severity of his signs and symptoms.

van Valen et al. (2009) reviewed the epidemiologic literature to provide an overview of the course and prognostic factors of chronic solvent encephalitis following exposure to solvents, but did not reach any definite conclusions and did not address the outcome of schizophrenia.

In summary, case reports, case series and case–case reports, despite many limitations, suggest some overlap between symptoms and signs of CSE and "negative signs" of schizophrenia (regarding memory loss and cognitive decline). The presence of psychotic symptoms ("positive signs") of schizophrenia, such as delusions, hallucinations and thought disturbances, distinguishes between these conditions.

Cohort-type studies suggest that exposures below regulatory thresholds may increase risks for subsequent neurotoxic and neurobehavioral impairment.

7. Discussion

The patient presented with nonspecific neurotoxic signs and symptoms, hospitalized and diagnosed first as suffering from acute psychosis; when it became clear that his condition was chronic, his diagnosis was established as schizophrenia. The case for causality between the patient's exposures and schizophrenia was based on the "weight of the evidence" approach to his history. The fact that the patient's acute symptoms appeared following his sustained and massive exposure to organic solvents, suggested that the exposure triggered schizophrenia. His symptoms were known to be produced by solvent exposure. The transient elevation of transaminases is the clinical evidence that his liver functions had been affected by exposure to solvents. The absence of findings on imaging is consistent with experience that imaging procedures cannot be relied upon as gold standard tests of brain disease from toxic exposures (Lubman et al., 2002). The fact that only 30% of the patients with schizophrenia have neuroradiologic abnormalities means that 70% do not.

The obscure circumstances in which the patient's brother disappeared and died, could possibly represent a familial factor which eventually caused him to be more susceptible to his occupational exposure to solvents, in such obviously appalling working conditions and in prolonged solitude. One should also note that his father was 43 years old when the patient was born, which is a borderline age in regard to the excess risk of schizophrenia, found over paternal age of 45 (Malaspina et al., 2001, see Table 2). These factors may have interacted with his exposures and added to his susceptibility.

This sequence of an intense, symptomatic exposure, directly followed by nonspecific neurotoxic symptoms accompanied by an acute psychotic state with signs and symptoms typical to schizophrenia, restates and strengthens the case for a cause–effect relationship.

In the light of the foregoing, we propose a two-stage model in which the patient's exposures led to organic psychosis and his organic psychosis then was later diagnosed, by all doctors who examined him, as schizophrenia. This two-stage model states the case for a model of genetic risk for schizophrenia being modified or triggered by a high exposure to neurotoxic agents, without which there either would have been no clinical expression, less severe expression, or onset later on in life, perhaps also triggered by extrinsic factors. We suggest that this model takes into account current paradigms of exposure-susceptibility.

We suggest the need to take into account the possibility that extreme external exposures can trigger disease – even a relatively

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uncommon disease such as schizophrenia, which has not been proven to be associated with this exposure – in persons in whom there is preexisting susceptibility.

Current psychiatric terminology posits a distinction between schizophrenia without any known organic or environmental trigger, and clinically identical syndromes associated with the exposure as the trigger (DSM-IV-TR, 2000).

We cannot confidently rule out the possibility that this patient's occupational exposure and the symptoms which led to the diagnosis of schizophrenia were a mere coincidence. However, this is not the first report of such a coincidence. The reproducibility of the association and the severity of the exposures in this patient make the play of chance an unlikely explanation.

This patient's case history reinforces the case for taking careful occupational histories of past exposures in patients with schizophrenia and other psychoses—a routine that is not always followed. More case–control studies are needed to explore the contributory role of neurotoxic exposures in triggering expression of organic mental syndromes in individuals with prior indications of susceptibility.

The pertinent questions are: If the exposures in this case were missed, in how many other patients diagnosed with schizophrenia were they not looked for? If the associations in this case were not reported, how many others have not been reported? How many patients diagnosed as having schizophrenia, have in fact developed the disease as a consequence of prior exposures, possibly following primary nonspecific neurotoxic signs and symptoms? If the associations in this case were not reported, how many others have not been reported? How many patients diagnosed as having schizophrenia, have in fact developed the disease as a consequence of prior exposures, possibly following primary nonspecific neurotoxic signs and symptoms? Did the label – schizophrenia – disable the diagnostician? Does making the diagnosis divert attention from possible triggers? We suggest that the current pathogenetic models of schizophrenia may not adequately take into account the role of high exposure at the level of the individual patient. One also has to recognize that at the global level, the absence of evidence on the proportional contribution of solvent exposures to schizophrenia, and for that matter, all so called organic psychoses and neurobehavioral impairments, should not be equated with evidence of absence. In the interim, there remains an ethical import to delay, and the case for action remains: to prevent exposures at the source to solvents and other neurotoxic agents, by substitution and enclosure.

Conflicts of interest

EDR and OB provided expert medical opinions in support of the case for a cause–effect relationship between patient's exposures and medical status, as part of their work in Hebrew University-Hadassah Medical Center. The case was settled out of court.

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